REMARKS/ARGUMENTS

I. Status of Claims and Formal Matters

Claims 1-8, 10 and 12-20 are pending in this application. Claim 1 is proposed to be amended with this response. Claims 4 and 10 are canceled. Upon entry of the proposed amendments, claims 1-3, 5-8, and 12-20 are pending with claims 1-3, 5-8, 12-13 and 16-20 under active consideration.

The amendments to claim 1 are fully supported by the specification as filed with exemplary support at page 6, lines 13-21 and claim 4. No new matter is added by the proposed amendment. Applicant respectfully requests entry of the proposed amendments.

II. Claim Objections

At page 2 of the Office Action, the Examiner objected to claims 1-8, 10-13 and 16-20 because the Markush group of FSH substances in claim 1 is missing an "or" or "and" and the Markush group of LH substances in claim 1 includes only one species.

Claim 1 is amended, *inter alia*, to include the term "and" in the Markush group of FSH substances and to specify "recombinant LH (recLH) in an amount equivalent to a daily subcutaneous dose of between 1 and 40 I.U. recLH per kg of bodyweight…" In view of the amendments to claim 1, the objections may be properly withdrawn.

III. Patentability Arguments

A. Claim Rejections

1) The Rejections of Claims 1-4, 6-8, 10-13, 16-17 and 20 Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-4, 6-8, 10-13, 16-17 and 20 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grondahl et al. (US 6,585,982) (hereinafter "Grondahl") in view of Matthieu et al. (US 2003/0092628) (hereinafter "Matthieu") and further in view of Hideyuki Ikenaga, The Clinical Significance of the Ratio in FSH/LH of Human Menopausal Gonadotropins in a Programmed Stimulation Regimen for IVF-ET, Acta Obst. Gynaec. JPN,

1995, Vol. 47, No. 11, pp. 1223-1229 (hereinafter "Ikenaga") and Christina Bergh, Recombinant follicle stimulating hormone, Hum. Reprod., 1999, Vol. 14, No. 6, pp. 1418-1419 (hereinafter "Bergh"). Applicants respectfully traverse this rejection.

According to the Examiner, Grondahl teaches a COH regimen comprising the administration of a GnRH agonist to suppress FSH and LH, follicle stimulation with FSH or human menopausal gonadotropin (hMG) (a mixture of FSH and LH derived from the urine of post-menopausal women), and induction of an LH surge using hCG, but fails to teach administration of a GnRH antagonist (or recombinant LH). The Examiner cites Matthieu as teaching the use of GnRH antagonists (ganirelix) to prevent premature LH surges and cites Ikenaga as teaching that a 3:1 ratio of FSH/LH achieved a higher rate of pregnancy, *inter alia*, than a 1:1 ratio of FSH/LH or FSH alone, in a GnRH agonist COH protocol. According to the Examiner, it would have been obvious to one of ordinary skill in the art to add the GnRH antagonist step of Matthieu to the method of Grondal and to make FSH:LH in a 3:1 ratio in the combined method of Grondal and Matthieu to achieve, *inter alia*, increased pregnancy rates

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the Examiner must provide a clear articulation of the reasons why the claimed invention would have been obvious, i.e., the Examiner must provide a reason one of ordinary skill in the art would have combined the cited references to arrive at the claimed invention. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. Finally, the references when combined must teach or suggest all the claim limitations. *See* MPEP § 2143. The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988).

Applicants respectfully submit that (1) the Examiner has failed to provide a reason one of ordinary skill in the art would have combined the cited references to arrive at the claimed invention and (2) the cited references, alone or in combination, fail to teach or suggest all the claim limitations. For at least these reasons, the Examiner has failed to establish a *prima facie* case of obviousness

a) Lack of Motivation to Combine the References

Applicants respectfully submit that the cumulative teachings of the prior art of record fails to provide motivation to the skilled person to arrive at the subject matter of the pending claims. In particular, the Examiner has failed to identify any motivation to co-administer recombinant LH with a GnRH antagonist and an FSH substance in a method of controlled ovarian hyperstimulation. As discussed below, no such motivation existed and, in fact, the skilled person would have been discouraged from such coadministration.

Grondahl is directed to post-retrieval maturation of eggs with a MAS compound (a compound which mediates the meiosis of oocytes). Apart from the additional maturation step with a MAS compound, the IVF protocol "is performed the usual way." Grondahl, col. 4, lines 9-10. In this regard, Grondahl recites then-current COH protocols, including the steps of (1) treatment with GnRH to suppress endogenous gonadotropin secretion and (2) treatment with "FSH, e.g. Gonal-F, Puregon or Humegon" to grow follicles. Grondahl, col. 3, lines 26-28. Gonal-F and Puregon are highly purified preparations of recombinant FSH. Humegon is a purified preparation of gonadotropins extracted from the urine of postmenopausal females. Thus, for the step of follicle maturation, Grondahl explicitly recites treatment with "FSH" and lists as examples, various preparations including recombinant FSH and urinary preparations. While the urinary preparation may comprise FSH and LH, it is clear from Grondahl that such preparation is cited for its FSH content. Consistently, the working examples of Grondahl teach only the use of recombinant FSH (in the absence of LH) to stimulate follicle growth. Nowhere does Grondahl explicitly or implicitly teach or suggest that LH (recombinant or otherwise) should be independently added to FSH preparations. Recombinant LH is not even disclosed in Grondahl and the coadministration of FSH and recombinant LH would require the skilled person to make an inventive leap which, as elaborated *infra*, was discouraged by the art.

Bergh, published at about the same time as the priority date of Grondahl, discusses the use of recombinant FSH preparations for stimulating follicular growth and speaks to the desirability of using recombinant FSH over urinary preparations such as that (Humegon) disclosed by Grondahl for such purpose. For example, Bergh discloses that recombinant FSH preparations are substantially free of protein contaminants and more importantly are "more effective than urinary FSH [preparations] in inducing follicular development." Bergh, p. 1418,

col. 2, last paragraph. The Examiner has no basis for concluding that the teachings of Bergh apply to recombinant LH as well, as Bergh does not discuss recombinant LH preparations and certainly does not disclose that such preparations would be more effective than urinary preparations in inducing follicular development.

Matthieu discloses the use of GnRH antagonists in methods of COH but expressly states that such antagonists are to be used with recombinant FSH. Matthieu contains no teaching or suggestion to modify the procedure by co-administering recombinant LH. Indeed, the background of Matthieu reflects the use of only recombinant FSH (no LH) in follicle maturation as state of the art at the time of the invention disclosed therein (*see e.g.*, paragraphs [0005] and [0007]). Moreover, Matthieu repeatedly states that the GnRH antagonist is administered together "with FSH" following "initial ovarian stimulation with FSH **alone**." Matthieu, paragraph [0015]). There is no suggestion in Matthieu of the desirability to add exogenous LH (whether recombinant or urinary in origin) – to the contrary, Matthieu discloses that in the case of GnRH antagonist COH protocols, "no relationship between LH serum levels and pregnancy outcome was found." Matthieu, paragraph [0034]. Accordingly, one of ordinary skill of the art would be discouraged from adding recombinant LH to the GnRH antagonist protocol disclosed therein to achieve better pregnancy outcome. Rather, Matthieu teaches a correlation between GnRH level and pregnancy outcome. Specifically, Matthieu teaches that at a given GnRH antagonist dose level, lighter women are exposed to relatively high level of GnRH antagonist with adverse effects on pregnancy outcome. *See, e.g.* Matthieu, Examples 3 and 4. To overcome this, Matthieu provides a weight-based formula for individualization of doses.

Finally, to the extent that the Examiner is relying on Ikenaga to provide motivation, the Examiner is reminded that Ikenaga was published in 1995, prior to the availability of recombinant LH, is directed to GnRH agonist COH protocols and is completely inapposite in view of the multitude of subsequent studies, as referenced in Bergh and as provided by Applicant in their prior reply, clearly demonstrating the clinical superiority of purified FSH, whether recombinant or urinary in original, over urinary preparations comprising both FSH and LH.

In sum:

- Grondahl teaches a method of COH using a GnRH agonist and FSH (recombinant or urinary in origin) but does not teach or suggest co-administration with recombinant LH
- Matthieu teaches a method of COH using a GnRH antagonist and recombinant FSH and teaches away from co-administration with LH (recombinant or otherwise)
- Bergh teaches the desirability of recombinant FSH (free of LH) over urinary preparations for stimulating follicle growth

In view of the aforementioned, it is clear that explicit or implicit motivation to co-administer recombinant LH with a GnRH antagonist and an FSH substance in a method of COH cannot be found in either the cited references or in the art. Accordingly, the Examiner has failed to make a *prima facie* case of obviousness and Applicants therefore request that the rejection of claims 1-4, 6-8, 10-13, 16-17 and 20 under 35 U.S.C. § 103(a) be withdrawn.

b) The Prior Art Fails to Teach or Suggest All the Claim Limitations

Moreover, the cited prior art, in combination, fails to teach or suggest the coadministration of **recombinant** LH at the specified concentration in combination with a GnRH antagonist at the specified concentration and an FSH substance in a method for COH. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The prior art references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. *See* MPEP § 2141.

Contrary to Examiner's statement, Grondahl does not disclose administration of LH, recombinant or otherwise, at the claimed dosage – rather, as mentioned above, Grondahl only discloses administration of LH implicitly in the recitation of Humegon (hMG) as one means of administering FSH to stimulate follicle growth. Humegon is a purified preparation of gonadotropins (comprising FSH and LH) extracted from the urine of postmenopausal females. Grondahl discloses that the concentration of FSH for stimulating follicle development should be

between 150-400 IU/day but does not disclose a range for LH concentration. At any rate, neither Grondahl nor any other cited reference teaches or provides any guidance which could lead the skilled person to the claimed dose range of 1 to 40 I.U./kg bodyweight administered daily.

Moreover, none of the cited prior art references teaches or suggests administration of a GnRH antagonist at the claimed dose range equivalent to 1.0 to 4.0 mg ganirelix administered daily. Rather, as discussed in Matthieu, GnRH antagonist concentrations of at least 1 mg were discouraged during COH: "[f]or the antagonist ganirelix for example a fixed amount being at least 0.125 mg but less than 1 mg and preferably about 0.25 mg was suggested (WO98/58657)" (emphasis added). Matthieu, paragraph [0007]. Nor does Matthieu teach or suggest the presently claimed dosage. Matthieu presents a weight-based formula (5.5*BW-166)+/-7%) for calculating GnRH antagonist dosage, with the optimal dose of ganirelix ranging between 128 μg (for women at 50 kg) and 264 μg (for women at 80 kg). *See* Table 2. According to the formula of Matthieu, a woman would have to be at least 467 pounds (+/-7%) to qualify for a 1 mg dosage of ganirelix.[1] However, such a woman would not be qualified to undergo COH, nor is such a woman contemplated by Matthieu.[2] Finally, with respect to the ranges cited by the Examiner (i.e., between 0.001 and 5 mg/kg; preferably between 0.01 and 1 mg/kg), the Examiner's attention is respectfully directed to the fact that these ranges are weight-based ranges rather than ranges of a fixed amount of GnRH antagonist as presently claimed. Moreover, based on the average female weight of 60 kg, the ranges cited by the Examiner lead to the absurd result of between 0.06 mg and 300 mg of GnRH antagonist, preferably between 0.6 mg and 30 mg GnRH antagonist. On the other hand, the weight-based formula of Matthieu, which is the inventive aspect of Matthieu and which is based on the working examples discloses a dose of 0.185 GnRH for a female weighing 60 kg which does not even fall within the preferred range cited by the Examiner. Accordingly, one of ordinary skill in the art, reading Matthieu, would be discouraged from administering a GnRH inhibitor at the presently claimed concentration.

[1] 5.5(212)-166+/-7% = 1000 μg. 212 kg is about 467 pounds.
[2] The heaviest woman administered GnRH antagonist in the working examples of Matthieu was just over 80 kg (equivalent to about 176 pounds). See also, Office Action, footnote 1, stating that "women typically weigh between 42 to 120 kg."

c) Conclusion

In sum, the cited references, alone or in combination, fail to establish a *prima facie* case of obviousness. At the very least, one of ordinary skill in the art would have been led in a direction divergent from that taken by Applicants in view of the prior art, which in totality, teaches away from the presently claimed invention. Applicants have demonstrated at least two independent and legally sufficient reasons for the Examiner to withdraw the rejections of claims 1-4, 6-13, 16-17 and 20 under 35 U.S.C. § 103(a) and Applicants request that the rejections be withdrawn.

2) The Rejections of Claims 1-4, 6-8, 10-13, 16-17 and 20 Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-8, 10-13 and 16-20 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Grondahl in view of Matthieu and further in view of Ikenaga and Bergh and further in view of Scott et al., Correlation of Follicular Diameter with Oocyte recovery and Maturity at the Time of Transvaginal Follicular Aspiration, Journal of in Vitro Fertilization and Embryo Transfer, 1989, Vol. 6, No. 2, pp. 73-75.

The failure of Grondahl, Matthieu, Ikenaga and Bergh to establish a prima facie case of obviousness is discussed *supra*. Scott, which according to the Examiner discloses "that the probability of retrieving a metaphase I or II oocytes (sic) was significantly lower in follicles <11 mm and only somewhat higher in 12-14-mm follicles and equally high among the other groups" fails to correct the aforementioned deficiencies of Grondahl, Matthieu, Ikenaga and Bergh. Accordingly, Applicants request that the rejections of claims 1-8, 10-13 and 16-20 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION.

Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below.

Respectfully submitted,

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